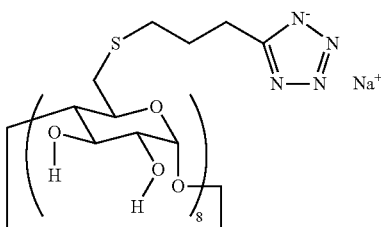


17

Per-6-deoxy-per-6-thio- γ -cyclodextrin (500 mg; Example 17), 3-bromo-2,2-dihydroxy-methylpropanol (670 mg), cesium carbonate (550 mg) and dimethylformamide (10 ml) were heated and stirred for 35 days at 65° C. until analysis by LCMS showed conversion to the required product. The mixture was evaporated to dryness, dissolved in water, dialysed against water, evaporated to low volume and precipitated with acetone. Drying under vacuum gave the title compound (550 mg).

Mass spec. FIA (M-H) 2369. ^1H NMR (D_2O): δ 2.84 (m, 16H), 3.15 (m, 8H), 3.24 (m, 8H), 3.69 (s, 64H), 3.85-4.19 (m, 16H), 5.25 (s, 8H).

EXAMPLE 19

6-Per-deoxy-6-per(3-(tetrazol-5-yl)propyl)thio- γ -cyclodextrin, Sodium Salt

Per-6-deoxy-per-6-thio- γ -cyclodextrin (1 g), 4-bromobutyronitrile (1 g), cesium carbonate (1 g) and dimethylformamide (10 ml) were stirred together at 60° C. over the weekend. The mixture was cooled, water added and the precipitate separated by centrifuge. After washing and drying the perbutyronitrile (1.4 g) was obtained. This product (1 g), sodium azide (1.3 g), triethylamine hydrochloride (2.8 g) and dimethylformamide (13 ml) were stirred and heated together for 7 days at 100° C. The mixture was cooled, diluted with water, acidified and the precipitate filtered off. This was washed with water, sonicated with methanol, separated by centrifuge, dried and dissolved in sodium hydroxide solution (M, 10 ml), filtered and dialysed to neutrality. This solution was evaporated to dryness to give the title compound (600 mg). Mass spec. (M-2H) 1152.8.

^1H NMR (D_2O): δ 1.95 (m, 16H), 2.55 (m, 16H), 2.85 (m, 24H), 3.05 (d, 8H), 3.5 (m, 8H), 3.6 (m, 8H), 3.9 (m, 16H), 5.06 (s, 8H).

EXAMPLE 20

Reversal of Neuromuscular Blockade in Anaesthetized Guinea Pigs in vivo

Male Dunkin-Hartley guinea pigs (bodyweight: 600-900 g) were anaesthetized by i.p. administration of 10 mg/kg pentobarbitone and 1000 mg/kg urethane. After tracheotomy, the animals were artificially ventilated using a Harvard small animal ventilator. A catheter was placed into the carotid artery for continuous monitoring of arterial blood pressure and the taking of blood samples for blood gas analysis. Heart rate was derived from the blood pressure signal. The sciatic nerve was stimulated (rectangular pulses of 0.5 ms duration at 10 s (0.1 Hz) intervals at a supramaximal voltage, using a Grass S88 Stimulator) and the force of M. gastrocnemius contractions was measured using a Grass FT03 force-displacement transducer. Contractions, blood pressure and heart rate were

18

recorded on a multichannel Grass 7D recorder. Catheters were placed in both jugular veins. One catheter was used for the continuous infusion of a neuromuscular blocking agent. The infusion rate of the neuromuscular blocking agent was increased until a steady-state block of 85-90% was obtained. The other catheter was used for administration of increasing doses of the reversal agent. During continuous infusion of the neuromuscular blocking agent, single doses of increasing concentration of reversal agent were given. At the end of the experiment, the measured force of muscle contractions was plotted against the concentration of reversal agent, and using regression analysis techniques, the 50% reversal concentration was calculated. Results for the reversal of the neuromuscular block, induced by the muscle relaxant rocuronium bromide (Roc), by the 6-mercapto-cyclodextrin derivatives of Examples 1-19 are presented in Table 1. For comparison, the reversal activity of the parent compounds β -cyclodextrin and γ -cyclodextrin are included as well.

TABLE 1

Dose (ED_{50} , $\mu\text{mol} \cdot \text{kg}^{-1}$) producing 50% reversal of steady-state neuromuscular block in anaesthetized guinea pigs and concentration at maximum reversal.		
Compound	ED_{50} $\mu\text{mol} \cdot \text{kg}^{-1}$	% max reversal at conc. ($\mu\text{mol} \cdot \text{kg}^{-1}$)
γ -cyclodextrin (γ -CD)	4	104 (47)
β -cyclodextrin (β -CD)	20	93 (113)
6-mono-deoxy-6-mono-(4-carboxyphenyl)-thio- γ -cyclodextrin, Na salt (example 1)	0.94	102 (8.0)
6-mono-deoxy-6-mono-(2-carboxyphenyl)-thio- γ -cyclodextrin (example 2)	1.30	93 (11)
6-per-deoxy-6-per-(3-carboxyphenyl)thio- γ -cyclodextrin (example 3)	0.28	102 (1.28)
6-per-deoxy-6-per-(2-carboxyethyl)thio- γ -cyclodextrin, Na salt (example 4)	0.09	97 (0.53)
6-per-deoxy-6-per-(5-carboxypentyl)thio- γ -cyclodextrin, Na salt (example 5)	0.74	78 (2.5)
6-per-deoxy-6-per-(3-carboxypropyl)thio- γ -cyclodextrin, Na salt (example 6)	0.09	108 (0.48)
6-per-deoxy-6-per-carboxymethylthio- γ -cyclodextrin, Na salt (example 7)	0.21	88 (1.92)
6-per-deoxy-6-per-(4-carboxyphenyl)thio- γ -cyclodextrin, Na salt (example 8)	0.10	95 (0.48)
6-per-deoxy-6-per-(4-carboxyphenylmethyl)-thio- γ -cyclodextrin, Na salt (example 9)	0.13	100 (0.50)
6-per-deoxy-6-per-(3-amidopropyl)thio- γ -cyclodextrin (example 10)	0.57	94 (33)
6-per-deoxy-6-per-(5-hydroxy-3-oxa-pentyl)-thio- γ -cyclodextrin (example 11)	0.47	92 (2.1)
6-per-deoxy-6-per-[(2(2 carboxybenzoyl)-amino)ethyl]-thio- γ -cyclodextrin, sodium salt (example 12)	0.085	95 (0.48)
6-per-deoxy-6-per-(2-hydroxyethyl)thio- γ -cyclodextrin (example 13)	0.20	96 (2.0)
6-per-deoxy-6-per-(N-methylamidomethyl)-thio- γ -cyclodextrin (example 14)	1.54	102 (7.3)
6-per-deoxy-6-per-(2-carboxypropyl)thio- γ -cyclodextrin, sodium salt. (example 15)	0.10	103 (0.48)
6-per-deoxy-6-per-(3-carboxypropyl)thio- β -cyclodextrin, sodium salt (example 16)	0.5	100 (3.2)
6-per-deoxy-6-per-(2-sulfoethyl)thio- γ -cyclodextrin, sodium salt (example 17)	0.055	106 (1.7)
6-per-deoxy-6-per-(2,2-di(hydroxymethyl)-3-hydroxy-propyl)thio- γ -cyclodextrin (example 18)	2.9	63 (4.9)
6-per-deoxy-6-per-(3-(tetrazol-5-yl)-propyl)thio- γ -cyclodextrin, sodium salt (example 19)	0.22	109 (1.2)